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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/805,804
Filing Date: March 22, 2004
Appellant(s): BAULCOMBE ET AL.

Kate H. Murashige
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 06 March 2009 appealing from the Office action mailed 29 July 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

In U.S. patent application serial number 11/013,316 a Notice of Appeal was filed 01 December 2008 and an appeal brief was filed on 04 May 2009.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each

dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because it states that the short RNA molecules (SRMs) have any number of nucleotides between 20 and 30 including 20-24. While the specification teaches that SRMs are 20-30 nucleotides in size, the size of the SRMs used in the method of the appealed claims is limited to consisting of 20, 21, 22, 23, or 24 nucleotides.

It is also noted that in response to an election of species requirement (restriction/election requirement mailed 07 July 2005), Appellants elected the species of plants (response filed 25 July 2005, paragraph bridging pages 17-18).

Appellant's summary of the claimed subject matter in the Appeal Brief also includes comments regarding the prior art and accomplishments of the instant inventors. In this section of the Answer, the Examiner is only addressing Appellant's summary of the claims.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,573,099	GRAHAM	6-2003
6,506,559	FIRE et al.	1-2003
7,723,897	BROWN et al.	4-2004

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 125-130 on appeal stand rejected under 35 U.S.C. 102(e) as being anticipated by Graham (U.S. Patent No. 6,573,099, issued June 3, 2003, filed June 19, 1998).

Independent claim 125 is broadly drawn towards a method of silencing a gene in cells by PTGS (post-transcriptional gene silencing), the method comprising introducing into cells a composition containing at least one vector that, when introduced into said cells, produces SRMs (short RNA molecules), which SRMs are SSRMs (short sense RNA molecules) and SARMs (short antisense RNA molecules), wherein said SARMs are complementary to a region of a target RNA transcribed from a gene silenced when said short RNA molecules are present in cells containing said gene, and said SSRMs correspond to said target RNA, and wherein the SSRMs and SARMs consist of 20, 21, 22, 23, or 24 nucleotides, whereby said gene is silenced. Independent claim 128 is broadly drawn to a method of silencing any gene in cells of an organism by PTGS, the method comprising introducing into said cells a composition containing at least one vector that, when introduced into said cells, produces SARMs and SSRMs corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which

consist of 20, 21, 22, 23, or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

Graham teaches isolated genetic constructs, and vectors comprising them, the construct comprising a synthetic gene comprising two copies of a structural gene sequence, wherein the structural gene sequence comprises a nucleotide sequence that is identical to a region of a target gene (col. 4, lines 24-67). The size of the structural gene sequences can be 20 to 30 nucleotides long (col. 6, lines 25-29), thus the nucleotide sequences may be 20, 21, 22, 23 or 24 nucleotides. One of the sequences is present in the sense orientation (and encodes what would be a short sense RNA molecule), the other in antisense (col. 7, lines 5-24) (and encodes what would be a short antisense RNA molecule), both operably linked to the same or individual promoters (col. 2, lines 37-48). Graham teaches a method of introducing the constructs into cells of a plant (col. 1, lines 7-14; col. 13, lines 57-67), wherein the expressed short RNA products encoded by the structural genes reduce the expression of the target gene, which may be any gene, including genes endogenous to the organism (col. 4, lines 40-45). The expressed short RNA product of the structural gene in antisense orientation inherently has the property of being capable of base pairing with complementary sequences in the target RNA. The expressed short RNA of the structural gene in sense orientation corresponds to the target RNA. Graham teaches each of the limitations of the steps of the instantly claimed method.

Claims 116-124 on appeal stand rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (U.S. Patent No. 6,506,559, issued January 14, 2003, filed December 18, 1998) in

view of Graham (U.S. Patent No. 6,573,099, issued June 3, 2003, filed June 19, 1998).

Independent claim 116 is broadly drawn towards a method of silencing a gene in cells (the elected species is plants) by post-transcriptional gene silencing (PTGS), comprising introducing into cells a composition containing short RNA molecules (SRMs) which are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) at the same abundance, wherein the SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said SRMs are present in cells containing said gene, and said SSRMs correspond to said target RNA, and wherein the nucleotide sequences of the SRMs consist of 20, 21, 22, 23, or 24 nucleotides, whereby said gene is silenced. Independent claim 120 is broadly drawn towards a method of silencing a gene in cells of an organism by PTGS, comprising introducing into said cells a composition of isolated SARMs and isolated SSRMs corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23, or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

Fire et al. teach a method of silencing a target gene post-transcriptionally in plant cells or plants, comprising introduction of a dsRNA wherein one of the strands is complementary to a portion of the target gene. The method comprises introducing into cells short RNA molecules that are complementary to each other and are in sense and antisense orientation with respect to a portion of the target gene sequence (col. 6, lines 32-43; col. 7, lines 30-31; col. 7, lines 53 to col. 8, line 6; col. 8, lines 13-35; claims). One of the short RNA molecules will therefore be complementary to a sequence in the target RNA transcribed from the gene, and the other will correspond to that sequence in the target RNA. The target gene may be any gene, including an

endogenous gene (col. 6, lines 44-45; claims). The RNA may be synthesized chemically (col. 8, line 62 to col. 9, line 25), indicating that synthetic RNA molecules are taught by the reference. As the sense and antisense RNA molecules form a double strand, they are present in equal abundance.

Fire et al. do not actually disclose RNA molecules that are 20, 21, 22, 23, or 24 nucleotides.

Graham teaches a method of expressing in plant cells sense sequences corresponding to a target gene, and antisense sequences complementary to said target gene, to repress expression of said gene, wherein the sense and antisense sequences can be 20-30 nucleotides long, as discussed above (col. 1, lines 7-14; col. 4, lines 24-67; col. 6, lines 25-29; col. 7, lines 5-24; col. 13, lines 57-67).

It would have been obvious and within the scope of one of ordinary skill in the art to modify the method of Fire et al. to introduce into plants double-stranded RNA molecules to inhibit expression of a target gene, by making the RNA molecules 20-24 nucleotides long. Graham teaches that expressed RNA sequences that repress expression of a target gene of interest can be 20-30 nucleotides long. It therefore would have been obvious to make the double-stranded RNA of Fire et al. 20, 21, 22, 23, or 24 nucleotides long, as they are all within 20-30 nucleotides in length and are considered functional equivalents. The nucleic acid fragments were synthetic, as their construction required recombinant DNA techniques.

Claims 116-130 on appeal stand rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (U.S. Patent No. 6,723,987, issued April 20, 2004, filed August 19, 1999).

Independent claim 116 is broadly drawn towards a method of silencing a gene in cells (the elected species is plants) by post-transcriptional gene silencing (PTGS), comprising introducing into cells a composition containing short RNA molecules (SRMs) which are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) at the same abundance, wherein the SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said SRMs are present in cells containing said gene, and said SSRMs correspond to said target RNA, and wherein the nucleotide sequences of the SRMs consist of 20, 21, 22, 23, or 24 nucleotides, whereby said gene is silenced. Independent claim 120 is broadly drawn to a method of silencing a gene in cells of an organism by PTGS, comprising introducing into said cells a composition containing isolated SARMs and isolated SSRMs corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23, or 24 nucleotides and wherein said SARMs can base pair with said target RNA. Independent claim 125 is broadly drawn towards a method of silencing a gene in cells by PTGS, the method comprising introducing into cells a composition containing at least one vector that, when introduced into said cells, produces SRMs, which SRMs are SSRMs and SARMs, wherein said SARMs are complementary to a region of a target RNA transcribed from a gene silenced when said short RNA molecules are present in cells containing said gene, and said SSRMs correspond to said target RNA, and wherein the SSRMs and SARMs consist of 20, 21, 22, 23, or 24 nucleotides, whereby said gene is silenced. Independent claim 128 is broadly drawn to a method of silencing any gene in cells of an organism by PTGS, the method comprising introducing into said cells a composition containing at least one vector that, when introduced into said cells, produces SARMs and SSRMs corresponding to a target RNA

transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23, or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

None of the appealed claims require the SARMs and SSRMs to be complementary to each other.

Brown et al. teach methods to inhibit the expression of an endogenous gene encoding an enzyme of the gibberellin (GA) synthesis pathway in plants (col. 3, lines 13-25). The method comprises expressing a coding sequence, or fragment thereof, of an enzyme of the GA synthesis pathway in the plant in antisense orientation (which would be complementary to a region of the target RNA), or in sense orientation (which would have the same sequence as and correspond to the target RNA) to cause co-suppression (col. 3, lines 49-67). Fragment sizes include those that are at least 20 or 24 nucleotides long (col. 5, lines 50-58). The nucleic acid fragment could be introduced into the plants from DNA or RNA expression vectors (col. 21, lines 57-63). Antisense-mediated and sense-mediated inhibition of gene expression are sequence-specific and are variations of post-transcriptional gene silencing. The RNAs produced can be considered synthetic as they are not isolated from nature.

Brown et al. do not exemplify using anti-sense and co-suppression strategies simultaneously to inhibit the expression of a target gene.

It would have been obvious and within the scope of one of ordinary skill in the art to modify the method of Brown et al. by expressing a fragment of a coding sequence of the GA synthesis pathway in the sense and antisense orientation at the same time. Note that the fragments need not target the same region of target gene. It would have been obvious to make the fragment sizes to be as short as 20-24 nucleotides, as this is within the size range taught by

Brown et al. All such fragment sizes are considered functional equivalents. The nucleic acid fragments were obviously synthetic, as their construction required recombinant DNA techniques. One would have been motivated to inhibit target gene expression by using antisense and co-suppression strategies at the same time, as the use of two strategies to inhibit gene expression would have given a greater likelihood of success. Claims 116-124 are included in the rejection, as the neither the claims nor the instant specification exclude from the composition introduced into the cells the presence of vectors expressing the SRMs.

(10) Response to Argument

Appellant's argument to the rejection of appealed claims 125-130 under 35 U.S.C. 102(e) over Graham, and Examiner's response:

Appellants argue that Graham only discusses a sequence or length in terms of DNA contained in vectors, never any length of RNA produced by such vectors; that even if the structural genes contained in Graham's synthetic genes were disclosed to contain only 20-30 nucleotides, this does not necessarily result in RNA transcripts having this same length. Appellants argue that RNA transcripts typically include, for example, polyadenylation signals and polyA itself, as is described in standard molecular biology textbooks, and this would extend the length of the RNA transcript beyond the length of the structural gene component. Appellants argue that in order to anticipate, generation of sequences of this length (presumably 20-24 nucleotides) by the constructs of Graham must be a certain and consistent result of expression (brief, paragraph bridging pages 5-6 and 1st full paragraph on page 6).

Appellants' argument was fully considered but was not persuasive. Graham in col. 13, lines 23-26 states, "Alternatively or in addition, the synthetic genes described supra may further comprise one or more transcription termination sequences placed at the 3'-end of the transcriptional unit of the synthetic gene sequence." Polyadenylation signals are located in such termination sequences, and polyadenylation occurs when transcription is mediated by RNA polymerase II. Further, Graham also teaches that preferred promoters include the bacteriophage T7 promoter (col. 8, line 24-25), and it was known before the instant priority date that polyadenylation does not occur in transcripts generated from it. The generation of RNA sequences lacking polyadenylation will occur if promoter systems not recognized by RNA polymerase II are used. Graham does not make polyadenylation a requirement, nor does the reference limit the type of promoter system that may be used in the constructs and method described therein. Col. 8, lines 24-25 also provide examples of bacteriophage promoters that can be used with the constructs. If a termination sequence comprising a polyadenylation signal is not present or required in the construct, clearly one skilled in the art would use a RNA polymerase/promoter system that does not require such a terminator.

Appellants continue, arguing the situation here is similar to *Net MoneyIn, Inc. v. VeriSign, Inc.*, 545 F3d 1359, (Fed. Cir. 2008), where a claim to a sequence of steps requiring five elements was found not anticipated even though all five elements were contained in the document. To obtain the sequence of steps or arrangement as set forth in the claim, elements from two different sequences of steps needed to be combined (brief, paragraph bridging pages 6-7). Appellants argue the Examiner combined a number asserted to be associated with a structural gene component of the synthetic gene, with another category- the RNA produced, and the RNA

produced will not necessarily be limited to the nucleotides transcribed directly from the structural gene component (brief, page 7, 1st full paragraph).

Appellants' argument was fully considered but was not persuasive. The situation here is not analogous to *Net MoneyIn, Inc. v. VeriSign, Inc*. Elements from different arrangements in Graham are not being combined to arrive at the arrangement of the instant claims. Constructs comprising the synthetic gene but lacking a terminator that causes polyadenylation of the produced transcript can be part of the same arrangement of elements in Graham.

Appellants also argue that there is a minimum size required of a structural gene sequence included in the Graham constructs that is taught, but allegedly ignored by the Examiner. Appellants point to col. 5, lines 9-15 for stating, "the only requirement being that the synthetic gene is substantially identical at the nucleotide sequence level to at least a part of the target gene, the expression of which is to be modified. By "substantially identical" is meant that the structural gene sequence of the synthetic gene is at least about 80%-90% identical to 30 or more contiguous nucleotides of the target gene." Appellants argue that the Examiner has given this teaching no weight, but allegedly continues to assert that the disclosure at col. 6, lines 25-40, which teaches that structural gene components of the synthetic gene comprise at least about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase, viral coat protein or visually-detectable gene somehow renders the requirements taught at col. 5 and reiterated at col. 6, lines 18-24 null and void. Appellants argue that at a minimum, these different sections of Graham render it ambiguous (brief, paragraph bridging pages 7-8).

Appellant's argument was fully considered but was not persuasive. The record shows that the Examiner did not "ignore" this argument previously. Rather, the Examiner

acknowledged Appellant's argument in the Advisory Action mailed 04 November 2008 and posited that a sequence of 30 nucleotides as a minimum length is apparently not a requirement, given the teaching at col. 6, lines 25-27. It is also noted that claims 11 and 12 of Graham limit the length of the nucleotide sequence, comprised in the structural gene, that is substantially identical to a region of a target gene to being 20 to 30 nucleotides in length. Apparently, Graham does describe structural gene sequences being 20 to 30 nucleotides in length. It is noted that Appellants in this argument also emphasize the word "component" in the recitation, "structural gene component" (brief, sentence bridging pages 7-8), perhaps to further their argument that the synthetic gene contains other components that would result in an expressed RNA being greater than 24 nucleotides. However, as noted above, a termination sequence containing a polyadenylation signal need not be present in the synthetic gene.

Appellants also argue that Graham does not meet the legal standard for anticipation of a smaller range by a much larger one that contains it. Citing *In re Baird*, 16 F3d, 280, 29 USPQ2d 1550 (Fed. Cir. 1994), Appellants argue that a genus does not even provide obviousness of a species that is not explicitly suggested by the document disclosing the genus. Appellants also argue that Graham does not meet the legal criterion for anticipation of a "range" as set forth in *Atofina v. Great Lakes Chem. Corp*., 441, F3d 991, 78 USPQ2d 1417 (Fed. Cir. 2006), and that the range taught by Graham is 20-1385 nucleotides (brief, page 8).

Appellants argument was fully considered but was not persuasive. As discussed above, Graham does contemplate the length of the nucleotide sequence comprised in the structural gene and substantially identical to a region of a target gene, to being 20 to 30 nucleotides in length. The court in *Atofina v. Great Lakes Chem. Corp*. also state "a very small genus can be a

disclosure of each species within that genus", citing *In re Petering*, 301 F.2d 676, 682 [133 USPQ 275] (C.C.P.A. 1962) and *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, [58 USPQ2d 1508] (Fed. Cir. 2001) ("[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited."). The genus of 20 to 30 nucleotides is small enough that one can immediately envisage each specie encompassed therein.

Finally, Appellants argue that lower numbers in Graham's range are actively taught away from. Appellants direct attention to 1) column 10 for stipulating that the total length of a multiple structural gene sequence should be no more than, at a maximum, 500-2000 bases and 2) col. 18, lines 27-38 for providing a construct with an inverted repeat of a BEV polymerase open reading frame under the control of a single promoter (brief, page 9, 1st and 2nd full paragraphs).

Appellant's argument was fully considered but was not persuasive. It is unclear how a teaching regarding the maximum size allowable affects the minimum size that is taught.

Appellant's arguments to the rejection of appealed claims 116-124 under 35 U.S.C. 103(a) over Fire in view of Graham, and Examiner's response:

In the final rejection mailed 29 July 2008, the Examiner indicated that because Fire et al. in col. 8, line 6 states that the length of the identical nucleotide sequences of the double stranded RNA *may be* at least 25 bases (emphasis added), that other lengths for the nucleotide sequence are not excluded (paragraph bridging pages 4-5). However, even if Fire et al. does exclude dsRNAs less than 25 base pairs in length, sense and antisense sequences 20-30 nucleotides in length are embraced by Graham, and introduction of RNA into cells is taught by Fire et al. The

Examiner mentions this because in the Appeal Brief on pages 9-14, Appellants essentially argue that the RNA molecules taught by Fire have nucleotide sequences which are not part of the complementary, double stranded sequences, and discuss this in terms of the double stranded region being 25 bases in length, whereas the instant claims limit the RNA molecules to being 20-24 nucleotides in length. This is also addressed this below.

Appellants direct attention to col. 7, line 53 to col. 8, line 6 of Fire, and argue that the disclosure does not say that the length of the RNA molecule itself can be as short as 25 bases, only that the length of the identical nucleotide sequences contained within the molecule must be at least 25 or more nucleotides. Appellants argue that the minimum length of the actual RNA molecules is not specified anywhere in Fire (brief, paragraph bridging pages 9-10 and 1st full paragraph of page 10).

Appellants' argument was fully considered but was not found persuasive. It appears that Appellants are interpreting the transitional phrase "containing" in the recitation "RNA containing a nucleotide sequences identical to a portion of the target gene are preferred for inhibition", such that the RNA molecules must contain nucleotide sequences in addition to nucleotide sequences that are identical or complementary to a region of the target gene. However, MPEP 2111.03 clearly teaches that the transitional phrase "containing" is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. Open- transitional phrases allow for additional elements or steps, but there is no requirement that such additional elements or steps MUST be present. Further, col. 4, lines 20-23 of Fire states, "The process comprises introduction of RNA with partial or fully double-stranded character into the cell or into the

extracellular environment." Apparently Fire does contemplate the RNA being fully double stranded.

Appellants also point to the transitional phrase "consisting essentially of" in claim 1 of Fire and argue that it does not imply a limitation on the minimum length of the RNA molecule, only a limitation on the minimum length of the portion that corresponds to the gene to be silenced (brief, paragraph bridging pages 10-11 to the last paragraph of page 11).

Appellants' argument was fully considered but was not found persuasive. As Appellants have pointed out on page 11 of the brief, "consisting essentially of" indicates that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention. There is no requirement that such unlisted ingredients MUST be present.

Appellants next review a portion of the prosecution history of the U.S. patent application that issued as Fire et al., arguing that "consisting essentially of" was introduced into the claims mid-prosecution, allegedly specifically to denote the absence of a loop between the sense and antisense sequences, to overcome a prior art reference, and should not be interpreted to imply an overall length of the size of RNA, (brief, page 12, 1st to 3rd full paragraphs).

Appellants' argument was fully considered. The Examiner will not comment on issues prosecuted in other applications for patent. Further, the guidance on how Examiners are to interpret transitional phrases is provided in MPEP 2111.03.

On page 13, 1st full paragraph to the paragraph bridging pages 14-15 of the brief, Appellants argue that if claim 1 of Fire is to be considered a basis for rejecting the instant claims for anticipation (the Examiner assumes this to be an unintentional error, as this is an obviousness

rejection) that it is critical for the Board to recognize that as initially filed, the only mention of nucleotide length in Fire was in dependent claim 10. Appellants go on to allege that the recitation, "consisting essentially of" in the claims of the Fire patent is new matter, and is only accorded the date in which it was first introduced into the claims (8 January 2002, which is in mid-prosecution of the U.S. patent application that issued as Fire).

Appellants' argument was fully considered. As Appellants allege the recitation is new matter, this becomes an issue of validity of patented claims, which the Examiner cannot address. Every patent is presumed to be valid under 35 U.S.C. 282 and MPEP 1701 instructs USPTO employees not to express an opinion as to the validity or invalidity of any claim in a U.S. patent, except for examination of reissue applications, reexaminations, or interference involving a patent. The Examiner does however note that, as discussed above, the specification of Fire is also being relied on for the rejection.

Appellants argue that even if Fire disclosed that RNA molecules used in PTGS could be as short as 25 nucleotides, that Fire "mandates" that RNA molecules be that length as an absolute minimum (brief, page 15, 1st full paragraph).

Appellants' argument was fully considered but was not persuasive. Fire et al. in col. 8, line 6 states that the length of the identical nucleotide sequences of the double stranded RNA *may be* at least 25 bases (emphasis added). The Examiner does not interpret the recitation, "may be" as "must be". However, even if Fire is considered to limit the minimum size of the double stranded RNAs to being 25 base pairs, the reference still teaches introduction of dsRNA into cells and organisms. Graham also teaches a method of expressing in plant cells and plants sense sequences corresponding to a target gene, and antisense sequences complementary to said target

gene, to repress expression of said gene. The nucleotide sequences that Graham teaches can be 20-30 nucleotides long. It would have been obvious to combine the references by introducing double-stranded RNA of 20, 21, 22, 23, or 24 nucleotides long into a cell, as they are all within 20-30 nucleotides in length.

Appellants argue that Graham teaches away from this suggesting that only the structural gene components, not the RNA produced from them, contain anywhere from 20 to 1385 nucleotides in each strand, and that such a large genus hardly suggests the 20-24 nucleotide RNA species that is required by the appealed claims.

Appellants' argument was fully considered but was not persuasive. As discussed above, Graham does contemplate that the structural gene component can be 20-30 length, and even limits it to this size in claim 12. Any specie within this small range is easily envisioned. Even if it were not, it would have been obvious to make the RNA sequences of any size taught by Fire et al. or Graham, including 20-24 nucleotides, to determine the optimal workable conditions. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Further, in cases where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). MPEP 2144.05. Further, as discussed above, Graham does not require the presence of a transcription terminator comprising a polyadenylation signal, and therefore the RNA produced will not comprise a poly A tail. If a termination sequence comprising a polyadenylation signal is not present in the construct, it would have been obvious

to one skilled in the art to use a promoter system that does not require such a terminator. The RNA of Fire, and the RNA produced by the synthetic genes of Graham, are both made of a sequence that is either in sense or antisense orientation to a sequence within the desired target RNA. It would have been obvious to combine Fire et al. and Graham, as the method disclosed in both references result in similar RNAs being present in a plant cell or plant that repress the expression of a target RNA.

Appellants next comment that neither Fire nor Graham suggests short RNA molecules as a particular embodiment in light of the known interferon problem in the art, as discussed by Appellants in the response mailed 28 September 2008. Appellants argue that had it been appreciated by Graham or Fire that such molecules are effectors of PTGS, they surely would have at least mentioned that it would be desirable either to produce or use molecules in that size class. Appellants note that the Examiner's response to this argument in the Advisory Action mailed 04 November 2008 was that the interferon response does not occur in plants, which is the species that was elected for examination. Appellants argue that the issue here is not what is being prosecuted, but that Fire exemplified nematodes, Graham exemplified constructs targeting mammalian genes, and both encompass vertebrate systems, and that one would expect concern of inducing the interferon response by long dsRNA to have led Fire and Graham to disclose a preference for short RNA molecules (brief, page 15 last paragraph and page 16, 1st full paragraph).

Appellants' argument was fully considered but was not persuasive. Fire does teach that the RNA molecules "may be" at least 25 bases (the instant specification at page 4, lines 4-14 teaches that short RNA molecules are 25 nucleotides plus or minus 1, 2, 3, 4, or 5 nucleotides),

and Graham does teach that structural gene components, which encode RNA, can be 20-30 nucleotides. It is also noted that the instant specification makes no mention whatsoever of the interferon response. If Appellants are attempting to rely on the avoidance of the interferon response as an unexpected result to overcome the rejection, the instant specification falls short. Further, again, the interferon response is not a concern in plants, which is also encompassed by both Fire and Graham and the instant claims. Furthermore, as Appellants pointed out earlier, Graham discusses possible problems that one may encounter when working with long synthetic genes (col. 10, lines 26-32), which one of ordinary skill in the art may view as a reason to avoid using long RNA molecules.

Appellants also argue that because Fire's comments regarding length pertain to externally administered RNA, and Graham teaches intracellular production of RNA, they effectively describe apples and oranges. Appellants again argue that RNA generated from constructs would be generated in the nucleus and processed prior to entering the cytoplasm, while externally administered RNA is sent directly to the cytoplasm. Appellants argue there is no reason to combine Fire and Graham because Graham is exclusively concerned with providing synthetic genes to a cell (brief, paragraph bridging pages 16-17 to page 19, 2nd full paragraph).

Appellants' argument was fully considered but was not persuasive. Graham does encompass transcribing in a cell a nucleotide sequence that can be 20-30 nucleotides long, that is complementary to a sequence found in a target gene, along with a copy of that sequence in sense orientation. As discussed above, Graham teaches that transcription terminators that have polyadenylation signals need not be present in the construct, and therefore the transcripts will not

contain the additional sequences. Such transcripts will have the same structures as the sense and antisense RNAs as taught by Fire et al.

Appellants argue that the mechanism of target gene downregulation is not envisioned by Graham and is not focused on post-transcriptional gene silencing (brief, pages 17-19).

Appellants' argument was fully considered but was not persuasive. The embodiments of Graham relied on for the rejection do produce sense and antisense RNAs, similar to the RNAs in Fire, and therefore one of ordinary skill would expect them to behave similarly.

On page 19, 2nd full paragraph of the brief Appellants argue that one embodiment of Graham (col. 10, lines 26-44), in relation to palindromic constructs, discusses the danger of forming hairpin loops, and therefore any RNA produced by Graham's constructs, including dsRNA, would be considered unwanted side effects.

Appellants' argument was fully considered but was not persuasive. This portion of Graham is in reference to long synthetic gene sequences containing inverted repeats only (lines 26-30).

Appellant's argument to the rejection of claims 116-130 under 35 U.S.C. 103(a) over Brown et al., and Examiner's response:

Appellants direct attention to col. 3, line 63 of Brown et al., and make three observations. Appellants argue that Brown refers to sequences or their complements, while the present invention requires the presence of both sense and antisense SRMs. Appellants argue that there is no teaching of gene silencing involving both sense and antisense RNA or generating both sense and antisense RNA (brief, page 22, 1st and 2nd full paragraphs; emphasis in the original).

Appellants' argument was fully considered but was not persuasive. It would have been obvious to modify Brown by using both antisense and co- suppression approaches together. One of ordinary skill would have expected the antisense and the sense sequences to still perform their respective functions, as they would if only one approach was used. One of ordinary skill in the art could have combined these two elements as instantly claimed by known methods and would not have expected a change in their respective functions, with the combination yielding nothing more than predictable results.

Appellants also argue that the numbers recited by Brown recite the DNA sequence to be expressed, not the RNA sequence to be produced, that the expression will occur in the nucleus, and that accoutrements of nuclear production of the RNA, including translation termination signaling, and processing that might take place in the transition from the nucleus to the cytoplasm, renders this inapplicable (brief, page 22, 3rd full paragraph).

Appellants' argument was fully considered but was not persuasive. There is no requirement in Brown that transcripts must contain translation termination signaling. It has been long established that it is transcription mediated by RNA polymerase II that will result in the addition of a poly A tail on a transcript in eukaryotic cells. Brown et al. do not place any requirements in the type of transcription system that must be used in the constructs of their method.

Appellants also argue that the suggestion of the enormous range between 12 nucleotides and a full-length reading frame does not suggest the specific 20-24 nucleotide RNAs required by the claims (brief, page 22, last sentence).

Appellants' argument was fully considered but was not persuasive. It would have been obvious to make the sequences of any size taught by Brown, including 20-24, to determine the optimal workable conditions. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Further, in cases where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). MPEP 2144.05.

Appellants' comments as secondary considerations, and Examiner's response:

In the paragraph bridging pages 4-5 of the Appeal Brief, Appellants comment that there was no understanding in the art that short RNA molecules mediate gene silencing in PTGS. Appellants point out that attached to their response filed on 29 September 2008 are exhibits demonstrating that co-inventor Dr. Baulcombe was awarded the Lasker Prize and the Franklin Institute Medal in Life Science in 2008 for this discovery. Appellants argue that the claimed invention is based on their own work that in every instance of PTGS, there was a correlation with the presence of short RNA molecules. Appellants argue that the present inventors discovered that these are the actual effectors of PTGS, this finding being universally confirmed in the literature (brief, page 19, last paragraph page and 2nd paragraph, page 20). Appellants make similar comments in part D of their arguments (page 23).

The Examiner certainly recognizes and applauds Dr. Baulcombe for receiving the aforementioned awards in 2008. The Examiner has a difficult task here of addressing Appellant's comments without appearing to dismiss both inventors' inspiring career

accomplishments. The patent references cited in the art rejections teach introducing RNA molecules, which are in sense or antisense orientation to a target gene, into cells or organisms for the purpose of decreasing the expression of the target gene. It is the Examiner's position as discussed above that the patents teach or make obvious the sizes of the RNAs, and the methods, of the instant claims. Appellants state on page 5, 1st full paragraph of the Appeal Brief, "Until the work of the present inventors established the presence of both sense and antisense short RNA's in plants undergoing PTGS, it was understood that such silencing required much larger RNA molecules" (emphasis added). However, the Examiner is not aware of prior art teachings showing or stating that PTGS requires the size of the dsRNA to be "long". Nor is the Examiner aware of any prior art suggesting or stating that those in the art actually did not believe that dsRNAs which were not "long" would fail to cause PTGS of a target gene, in organisms susceptible to the interferon response, or in any other organism having a PTGS pathway. Further, the instant claims do not recite that the sense and antisense RNAs are complementary to each other. The patent documents cited in the rejections do include use of RNAs that are 20-30 nucleotides long, and for the reasons discussed above, render the claims obvious or anticipated. It is also noted that secondary considerations do not apply to rejections under 35 U.S.C. 102 (MPEP 2131.04).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Ashwin Mehta/

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/Anne Marie Grunberg/

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